

Review of: "Targeting Cancer Cell Signaling Using Precision Oncology Towards a Holistic Approach to Cancer Therapeutics"

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Potential competing interests: No potential competing interests to declare.

Kumar proposed a very detailed manuscript describing the main cell signaling pathways and molecular alteration involved in the pathogenesis of tumors and used as therapeutic targets. The authors described several aspects related to cancer development, progression and treatment, however, this generates great confusion in the readers as it is not clear what is the main topic of the paper. In the present form, the manuscript cannot be accepted for publication, but it is encouraged its resubmission after substantial revisions. Please see some minor/major issues that when addressed could improve the quality of the manuscript:

- 1) The manuscript needs English editing performed by a native speaker. In some parts there are too many adjectives and long sentences that should be avoided;
- 2) The following sentence is misleading: "The survival rates for cancer types that are responsive to therapy surpass 90% in developed countries, and the prognosis for several other cancer types that were considered the deadliest diseases earlier has improved noticeably in recent years, thanks to the rapid advances realized in clinical oncology over the years. [8][9].". The survival rates of responsive tumors depend greatly on the type of tumor and the time of follow-up. Survival rates higher than 90% are observed only in specific subtypes of tumors (e.g. luminal A breast cancer) only in case of early diagnosis. Please be more cautious in your statements and revise the sentence accordingly;
- 3) Provide references for the following paragraph of the Introduction section: "Rigorous cancer research in the past few decades supported by advances in cell and molecular biology has led scientists to clearly understand there are genetic changes associated with cancer incidences that cause the disease to grow and spread to other parts of the body. Cancer is initiated as the result of uncontrolled cell division and proliferation leading to tumor formation which culminates in metastasis that involves the dissemination of tumor cells to new sites in the body forming secondary tumors, and is responsible for about 90% of cancer-related deaths in reality. Cell proliferation requires a balanced rate of cell growth and division to maintain the increase in cell numbers for growth and development, maintenance of tissue homeostasis and wound healing. The fundamental abnormality leading to cancer development is unwanted cell proliferation due to an absence of balance between cell divisions and cell loss through cell death and differentiation. The division relies on cell cycle regulation that generally involves extracellular growth-regulatory signals as well as internal signaling proteins monitoring the genetic integrity of the cell to ascertain that cellular developments go well in time. It depends on

progression through distinct phases of the cell cycle-regulated by several cyclin-dependent kinases (CDKs) that act in association with their cyclin partners. Alterations in the overall expression pattern of cyclins lead the cellular process to go awry resulting in tumor formation.”;

4) A lot of information is repeated twice or several times throughout the text. You are encouraged to significantly shorten your manuscript avoiding redundancy;

5) In the manuscript you well-describe the selective inhibitors currently used for the targeted therapy of tumors. However, no descriptions were provided about the mechanisms of action of standard chemotherapy as well as the drug used (e.g. antimetabolites, alkylating agents, mitotic inhibitors, etc.). Please add these fundamental materials. For this purpose, please see:

- <https://doi.org/10.1016/j.cell.2023.02.038>

- <https://doi.org/10.1002/mco2.55>

- <https://doi.org/10.1158/0008-5472.CAN-17-2782>

- <https://doi.org/10.1016/j.tranon.2021.101056>

6) The manuscript is too long and the reader easily loses the main topic of the paper. It is suggested to split the paper into two different manuscripts, one describing the molecular alterations and signal transduction pathways involved in cancer development and progression and the second describing the techniques and pharmacological strategies used to diagnose and treat tumors;

7) In Chapter 5, you have to add a description of cell survival and apoptosis pathway. In addition, a paragraph on the epithelial-to-mesenchymal transition should be added;

8) I suggest to remove Chapter 6 or, at least, to particularly summarize the contents of Chapter 6 and move it to the Conclusion section as a future perspective. Same comment for Chapter 7.